Reconsideration of the application is requested in light of the amendments and the following remarks.

Rejection under 35 U.S.C. § 112, first paragraph

The specification is believed to provide an enabling disclosure in respect of the amended claims.

Applicant asks the Examiner to note that they have amended the independent claims by replacing the recitation of "a polypeptide consisting of at least 6 amino acids of sequence of tetanus toxin fragment C" with "tetanus toxin fragment C." This change renders moot the question of whether the specification enables a peptide as claimed containing only 6 amino acids of fragment C.

In order to provide an enabling disclosure in respect of the amended claims the specification must enable a fusion polypeptide comprising (i) tetanus toxin fragment C, fused to (ii) a polypeptide consisting of at least 6 contiguous amino acids of sequence of pre-S1 of hepatitis B virus (HBV), wherein the fusion polypeptide induces antibody that recognizes pre-S1 of HBV. Applicant submits that the specification does enable such a fusion polypeptide. The specification clearly demonstrates that such a polypeptide does induce antibody that recognizes pre-S1 of HBV.

In the Office Action, the Examiner argued that the specification only provides an enabling disclosure in respect of certain fusion proteins comprising specific pre-S1 sequences, namely the "pre $S1_{ayw}$ 20-47 or pre $S1_{ayw}$ 120-147" sequence. However, the Examples in the specification in fact show positive results spanning across the pre-S1 region, not just certain specific parts of the region. The pre-S1 region is 119 amino acids in length, and the Examples show positive results with polypeptides spanning amino acids 21-47, 21-119, 42-119, and 1-119 (see Table 2 on page 18). Thus, the results in the Examples remove the

unpredictability; they w uld allow a skilled person to predict with confidence that reasonable fusions between a pre-S1 sequence and fragment C would induce antibody against the pre-S1 sequence.

The Examiner states that "the fusion protein of pTECH3/S1/S2(preS1$_{ayw}$ 21-47/preS2$_{ayw}$1-55$_{aa}$) as disclosed in the specification does not produce an antibody against S1(20-47, see Table 2 on page 18)" (page 4 of the Office Action). Applicant respectfully points out that this is not an accurate statement. The relevant box in Table 2 contains "ND", which stands for "not done" (see the last line on page 18). Thus, Table 2 does not show failure to produce antibodies against pre-S1(20-47), but rather it simply shows that no experiment was done to determine whether an anti pre-S1(20-47) antibody was able to recognize the pTECH3/S1/S2 fusion protein.

In fact, Table 2 shows that in all cases where an experiment was done a positive result was obtained. Thus, the application does show that the fusion proteins according to the invention are predictably able to bind antibodies.

The Examiner cites a paper by Young et al. which describes a comparative clinical trial of a triple antigen vaccine (the HEPACARE vaccine) and a single antigen vaccine (Merck's Recombivax-HB vaccine). The Examiner notes that the single antigen vaccine protected a lower proportion of subjects than the triple antigen vaccine; the single antigen vaccine protected 83% of subjects whereas the triple antigen vaccine protected 97% of subjects using the best dosage regimen. The Examiner concludes from this that use of pre-S1 as a single antigen is unpredictable.

However, the protection of 83% of subjects by the single antigen vaccine is a good level of protection. Indeed, the vaccine (Recombivax-HB) is licensed for use in humans. Thus, contrary to the Examiner's position, Young et al. demonstrates that a single antigen vaccine against hepatitis B can be highly

effective. It may be true that the triple antigen vaccine is even more effective, but that does not detract from the fact that the single antigen vaccine by itself is effective.

In any event, the claims do not require that the polypeptides are effective as vaccines; they merely require that they are able to induce antibody that recognizes pre-S1. As explained above, the data in the specification show that the claimed polypeptides are indeed able to induce such antibody. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection of the claims under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. § 103

Applicant submits that there are at least three reasons why the claimed subject matter was not obvious. Firstly, there is no obvious reason why a skilled person would have focussed simultaneously and specifically on the disclosure about fragment C in Khan et al. and the disclosure about pre-S1 in Mimms et al. and on the disclosure in Shi et al. Secondly, it was not reasonably predictable that the claimed fusion proteins would produce a good antibody titer against the pre-S1 sequence and, indeed, Shi et al. would have led a skilled person to predict that such an antibody titer would not be achieved. Thirdly, the specification contains unexpected results; the results in the Examples show that the claimed fusion proteins produce a high antibody titer, and this would not have been expected in view of Shi et al. and the other references cited by the Examiner. Applicant will explain each of these three reasons in more detail below.

As a general rule, in order for a claimed invention to be obvious over a combination of references, it must have been obvious for a person skilled in the art to have combined the references prior to the date of invention. In other words, there must hav been some obvious reason for a skilled person to consider all the

references simultaneously and to hold the teaching of all of them in the forefront of his/her mind at the same time. In the present case, there was no obvious reason why a skilled person would have focussed simultaneously and specifically on the disclosure about fragment C in Khan et al. and the disclosure about pre-S1 in Mimms et al. and on the disclosure in Shi et al. The Examiner has failed to suggest any such obvious reason. Applicant submits that the absence of such a reason is by itself a demonstration that the claimed invention was not obvious.

In the Office Action, the Examiner notes that Applicant argued in the response to the previous Office Action that there were a vast number of combinations of carrier and antigenic sequence that could in theory have been dreamt up by a person skilled in the art and that, out of all the possible combinations, there was no obvious motivation to focus on both fragment C and pre-S1 and put them together (page 2 of the Office Action). Although the Examiner notes Applicant's previous arguments on this point, the Examiner does not find any criticism to make of them; the Examiner jumps straight from a summary of the arguments to the Khan et al. reference and the Mimms et al. reference without making any attempt to explain why it would have been obvious to a skilled person to make this combination of references. Applicant respectfully submits that the absence of any such explanation means that the Examiner has failed to make out a proper case for obviousness.

Turning now to the second reason for non-obviousness, it was not reasonably predictable that the claimed fusion proteins would produce a good antibody titer against the pre-S1 sequence and, indeed, Shi et al. would have led a skilled person to predict that such an antibody titer would not be achieved. In making the rejection of lack of enabling disclosure, the Examiner states that "it is unpredictabl whether each of designed fusion protein is able to produce an

enhanced immunity." However, the Examiner fails to take account of this unpredictability in reasoning on the issue of obviousness.

As explained in Dr Page's Declaration, the unpredictability of the art manifests itself in the Shi et al. paper cited by the Examiner. Shi et al. describes fusion of cholera toxin B subunit (CTB) to pre-S2 epitope. The fusion protein produced an extremely low antibody titre against the pre-S2 region. This is clear from, for example, Figure 7 on page 936 of Shi et al. The Figure shows that the peak antibody titre against CTB was about 5000, whereas the peak titre against pre-S2 was only about 140. A different scale had to be used for the anti-pre-S2 titre compared to that for the anti-CTB titre in order to present the anti-pre-S2 titre on the graph. The peak anti-pre-S2 titre was about 35 times less than the peak anti-CTB titre. Thus, Shi et al. would have led a skilled person to predict no success in fusing pre-S sequences to carrier proteins.

As regards the third reason for non-obviousness, the Examiner states that there are "no unexpected results" (page 3 of the Office Action). Applicant respectfully points out that the specification does in fact contain such results. The Examples shows that an unexpectedly high antibody response can be induced against pre-S by the fusion proteins that are the subject of the application. For example, the results presented in Figure 3B show that, seven days after a booster dose, the fusion proteins induced a good antibody titer against a pre-S1 peptide. The titer is of the same order of magnitude as that against the fragment C component of the proteins (see Figure 2B). These results would not have been expected from a reading of Shi et al. and the other references mentioned by the Examiner. Indeed, Shi et al. teaches against any expectation of such results; it teaches that an extremely low antibody titer is to be expected. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection of the claims under 35 U.S.C. § 103.

Amendment and Response
Applicant: Steven Neville Chatfield
Serial Number: 09/527,919

Attorney Docket: KCO1002US

In view of the above amendments and remarks, Applicant respectfully requests that the rejections of the claims be withdrawn. It is respectfully submitted that the application is in condition for allowance, and a notice to that effect is requested.

If any additional fees are due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 16-2312. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our deposit account.

Respectfully submitted,

Date: November 8, 2002

By _____

Customer No. 009561
Thomas E. Popovich, Esq. (30,099)
Patrick J. O'Connell, Esq. (33,984)
POPOVICH & WILES, P.A.
IDS Center, Suite 1902
80 South 8th Street
Minneapolis, MN 55402
Telephone: (612) 334-8989
Attorneys for Applicant

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Steven Neville Chatfield	Attorney Docket: KCO1002US
Serial No.:	09/527,919	Group Art Unit: 1648
Filed:	March 17, 2000	Examiner: Bao Qun Li
For:	HEPATITIS B VIRUS POLYPEPTIDES	

MARKED-UP VERSION OF AMENDED CLAIMS

35. (Amended) A fusion polypeptide comprising

(i) [a polypeptide consisting of at least 6 contiguous amino acids of sequence of] tetanus toxin fragment C, fused to

(ii) a polypeptide consisting of at least 6 contiguous amino acids of sequence of pre-S1 of hepatitis B virus (HBV),

wherein the fusion polypeptide induces antibody that recognizes pre-S1 of HBV.

38. (Amended) A fusion polypeptide according to claim 35 wherein the [polypeptide consisting of at least 6 contiguous amino acids of sequence of] tetanus toxin fragment C and the polypeptide consisting of at least 6 contiguous amino acids of sequence of pre-S1 of HBV are joined by a hinge linker.

41. (Amended) An immunogenic composition comprising a pharmaceutically acceptable carrier or diluent and a fusion polypeptide comprising

Certificate of Facsimile Transmission (37 C.F.R. § 1.8(a))
I hereby certify that 15 pages including cover are being facsimile transmitted to the Patent and Trademark Office on the date sh wn below:

Date: November 8, 2002 **Signature:** Patrick J. O'Connell

Name: Patrick J. O'C nnell

(i) [a polypeptide consisting of at least 6 contiguous amino acids of sequence of] tetanus toxin fragment C, fused to

(ii) a polypeptide consisting of at least 6 contiguous amino acids of sequence of pre-S1 of hepatitis B virus (HBV),

wherein the composition induces antibody that recognizes pre-S1 of HBV.

44. (Amended) An immunogenic composition according to claim 41 wherein the [polypeptide consisting of at least 6 contiguous amino acids of sequence of] tetanus toxin fragment C and the polypeptide consisting of at least 6 contiguous amino acids of sequence of pre-S1 of HBV are joined by a hinge linker.